

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61K 38/13, 31/436, A61P 27/02	A1	(11) International Publication Number: WO 00/38703 (43) International Publication Date: 6 July 2000 (06.07.00)
(21) International Application Number: PCT/JP99/07161 (22) International Filing Date: 20 December 1999 (20.12.99) (30) Priority Data: 60/113,939 24 December 1998 (24.12.98) US (71) Applicants (for all designated States except US): R-TECH UENO, LTD. [JP/JP]; 2-4-8, Koraihashi, Chuo-ku, Osaka-shi, Osaka 541-8543 (JP). FUJISAWA PHARMACEUTICAL CO., LTD. [JP/JP]; 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8514 (JP). (72) Inventor; and (75) Inventor/Applicant (for US only): UENO, Ryuji [JP/US]; 9476 Turnberry Drive, Potomac, Montgomery, MD 20854 (US). (74) Agent: TAKASHIMA, Hajime; Yuki Bldg., 3-9, Hiranomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-0046 (JP).	(81) Designated States: AL, AU, BR, CA, CN, CZ, HU, IL, IN, JP, KR, LT, LV, MK, MX, NO, NZ, RO, RU, SI, TR, US, ZA, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(54) Title: AGENT FOR TREATING VISUAL CELL FUNCTION DISORDER (57) Abstract The present invention provides an agent for treating visual cell function disorder containing an interleukin inhibitor such as macrolide compound, particularly FK506.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

DESCRIPTION

AGENT FOR TREATING VISUAL CELL FUNCTION DISORDER

TECHNICAL FIELD OF THE INVENTION

The present invention relates to an agent for treating visual cell function
5 disorder.

BACKGROUND OF THE INVENTION

In the structure of the eye, retina is present in the eyeground and controls the function of the eye to recognize the presence or absence and shape of an object by the presence of a visual cell layer of retina. In recent years, patients with eye
10 diseases undergo objective test of retinal function by the determination of electroretinogram (hereinafter sometimes referred to merely as ERG) and the determination is utilized for the diagnosis of the condition. The ERG consists of a-wave, b-wave, c-wave and the like, and a-wave is considered to mainly reflect the function of visual cells, b-wave is considered to reflect the function of bipolar cell
15 layer (mainly Müller cells) and c-wave is considered to reflect the function of retinal pigment epithelium. When the retinal function is damaged for some reason, it appears as changes in the peak latency and amplitude of each wave. For example, in the case of diabetic retinopathy, it is known that peak latency of each wave is extended from the early stage and the amplitude is attenuated; all waves are
20 attenuated and disappear in degenerative disease of retina, such as pigmentary retinal degeneration; and each wave becomes attenuated depending on the stages of disease in retinoblastic disorder such as central retinal artery occlusion, central retinal vein thrombosis, fundus hypertonicus, retinal detachment and the like. While the b-wave and the like are originated from the source located more
25 toward the central side of the retina than the visual cell from which the a-wave is originated, when the light reaches the retina, the visual cell is first excited and the b-wave and the like are first generated when the excitement is transmitted to the retinal cells on the central side. Therefore, even when the source of origin is other than visual cell, the waves are under strong influence of the function of the visual
30 cell. In other words, when the function of visual cell is damaged, ERG components become abnormal even if the source of origin of the b-wave and the like is normal. Therefore, in ERG, a-wave is the most important component, and if changes in peak latency and amplitude of a wave, which are caused by the

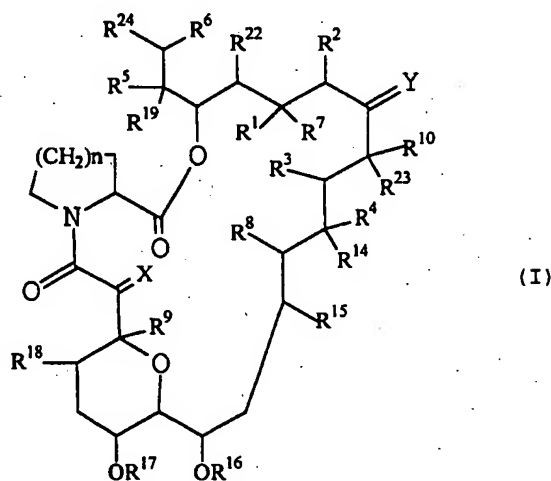
damaged function of visual cell, can be suppressed or recovered, the visual cell function disorder is expected to be effectively treated.

SUMMARY OF THE INVENTION

The present inventor has conducted intensive studies and surprisingly
 5 found that interleukin 2 (hereinafter sometimes referred to simply as IL-2) inhibitor has superior improving effect on visual cell function disorder and exhibit superior therapeutic effect on the diseases associated with visual cell function disorder, which resulted in the completion of the present invention.

Accordingly, the present invention provides the following.

- 10 (1) An agent for treating visual cell function disorder comprising an interleukin 2 inhibitor as an active ingredient.
- (2) The agent of (1), wherein the interleukin 2 inhibitor is a macrolide compound or a cyclosporin.
- (3) The agent of (2), wherein the macrolide compound is a tricyclo compound (I) of
 15 the following formula



wherein adjacent pairs of R^1 and R^2 , R^3 and R^4 , and R^5 and R^6 each independently

a) consist of two adjacent hydrogen atoms, wherein R^2 is optionally alkyl, or

b) form another bond optionally between carbon atoms binding with the

20 members of said pairs ;

R^7 is hydrogen atom, hydroxy, protected hydroxy or alkyloxy, or may form oxo with R^1 ;

R^8 and R^9 each independently show hydrogen atom or hydroxy ;

R¹⁰ is hydrogen atom, alkyl, alkyl substituted by one or more hydroxy, alkenyl, alkenyl substituted by one or more hydroxy or alkyl substituted by oxo ;

X is oxo, (hydrogen atom, hydroxy), (hydrogen atom, hydrogen atom), or a group of the formula -CH₂O- ;

5 Y is oxo, (hydrogen atom, hydroxy), (hydrogen atom, hydrogen atom), or a group of the formula N-NR¹¹R¹² or N-OR¹³ ;

R¹¹ and R¹² each independently show hydrogen atom, alkyl, aryl or tosyl ;

R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²² and R²³ each independently show hydrogen atom or alkyl ;

10 R²⁴ is an optionally substituted ring that may contain one or more hetero atom(s) ; and

n is 1 or 2.

In addition to the meaning noted above, Y, R¹⁰ and R²³ may show, together with the carbon atom they bind with, a saturated or unsaturated 5 or 6-membered
15 heterocyclic group containing nitrogen atom, sulfur atom and/or oxygen atom, the heterocyclic group being optionally substituted by one or more group(s) selected from alkyl, hydroxy, alkyloxy, benzyl, a group of the formula -CH₂Se(C₆H₅), and alkyl substituted by one or more hydroxy, or a pharmaceutically acceptable salt thereof.

20 (4) The agent of (2) or (3), wherein the macrolide compound is FK506.

(5) The agent of any of (1) to (4), which is used for the treatment of retinopathy.

(6) The agent of (5), wherein the retinopathy is ischemic retinopathy.

(7) The agent of (6), wherein the ischemic retinopathy is diabetic retinopathy.

(8) The agent of any of (1) to (7), which is in the form of a preparation for local
25 administration to the eye.

(9) A method for treating visual cell function disorder, comprising administering an effective amount of an interleukin 2 inhibitor to a subject in need of the treatment of visual cell function disorder.

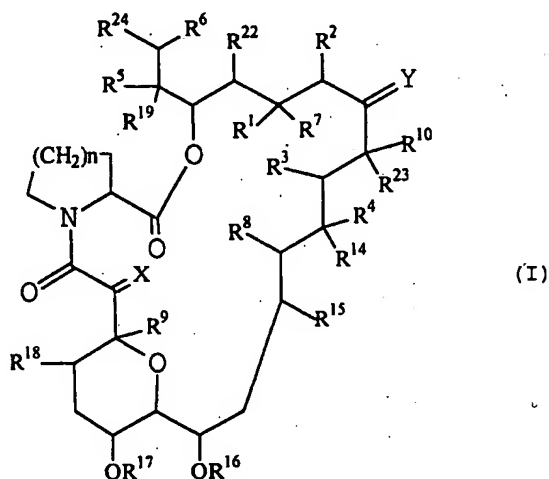
(10) Use of an interleukin 2 inhibitor for the production of a pharmaceutical
30 composition for the treatment of visual cell function disorder.

DETAILED DESCRIPTION OF THE INVENTION

The IL-2 inhibitor to be used in the present invention is not particularly limited and may be any as long as it has an IL-2 inhibitory activity. One example

thereof is IL-2 production inhibitor. Other example is IL-2 signal transduction inhibitor. Preferable examples thereof include macrolide compounds such as FK506, Ascomycin derivative, Rapamycin derivative and the like and cyclosporins and the like.

- 5 Specific examples of macrolide compound include tricyclo compound (I) of the following formula and a pharmaceutically acceptable salt thereof.



- wherein adjacent pairs of R¹ and R², R³ and R⁴, and R⁵ and R⁶ each independently
- a) consist of two adjacent hydrogen atoms, wherein R² is optionally alkyl, or
 - 10 b) form another bond optionally between carbon atoms binding with the members of said pairs ;
- R⁷ is hydrogen atom, hydroxy, protected hydroxy or alkyloxy, or may form oxo with R¹ ;
- R⁸ and R⁹ each independently show hydrogen atom or hydroxy ;
- 15 R¹⁰ is hydrogen atom, alkyl, alkyl substituted by one or more hydroxy, alkenyl, alkenyl substituted by one or more hydroxy or alkyl substituted by oxo ;
- X is oxo, (hydrogen atom, hydroxy), (hydrogen atom, hydrogen atom), or a group of the formula -CH₂O- ;
- Y is oxo, (hydrogen atom, hydroxy), (hydrogen atom, hydrogen atom), or a group
- 20 of the formula N-NR¹¹R¹² or N-OR¹³ ;
- R¹¹ and R¹² each independently show hydrogen atom, alkyl, aryl or tosyl ;
- R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²² and R²³ each independently show hydrogen atom or alkyl ;

R^{24} is a optionally substituted ring that may contain one or more hetero atom(s) ; and
n is 1 or 2.

In addition to the meaning noted above, Y, R^{10} and R^{23} may show, together with the carbon atom they bind with, a saturated or unsaturated 5 or 6-membered heterocyclic group containing nitrogen atom, sulfur atom and/or oxygen atom, wherein the heterocyclic group may be substituted by one or more group(s) selected from alkyl, hydroxy, alkyloxy, benzyl, a group of the formula $-CH_2Se(C_6H_5)$, and alkyl substituted by one or more hydroxy.

10 Preferable R^{24} is, for example, cyclo(C_5-C_7)alkyl optionally having suitable substituent, such as the following.

(a) 3,4-dioxocyclohexyl ;

(b) 3- R^{20} -4- R^{21} -cyclohexyl,

wherein R^{20} is hydroxy, alkyloxy or $-OCH_2OCH_2CH_2OCH_3$, and

15 R^{21} is hydroxy, $-OCN$, alkyloxy, heteroaryloxy having suitable substituent, $-OCH_2OCH_2CH_2OCH_3$, protected hydroxy, chloro, bromo, iodo, aminooxalyloxy, azide, p-tolyloxythiocarbonyloxy, or $R^{25}R^{26}CHCOO-$ (wherein R^{25} is hydroxy optionally protected where desired or protected amino, and R^{26} is hydrogen atom or methyl,
20 or R^{20} and R^{21} in combination form an oxygen atom of epoxide ring) ; or

(c) cyclopentyl wherein cyclopentyl is substituted by methoxymethyl, optionally protected hydroxymethyl where desired, acyloxymethyl (wherein acyl moiety is optionally quaternized dimethylamino or optionally esterified carboxy), one or more optionally protected amino and/or hydroxy, or
25 aminooxalyloxymethyl. Preferable example includes 2-formyl-cyclopentyl.

The definition of each symbol used in the formula (I), specific examples thereof and preferable embodiments thereof are explained in detail in the following.

"Lower" means that a group has 1 to 6 carbon atoms unless otherwise indicated.

30 Preferable examples of the alkyl moiety of "alkyl" and "alkyloxy" include linear or branched fatty hydrocarbon residue, such as lower alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, neopentyl, hexyl and the like).

Preferable examples of "alkenyl" include linear or branched fatty

hydrocarbon residue having one double bond, such as lower alkenyl (e.g., vinyl, propenyl (e.g., allyl and the like), butenyl, methylpropenyl, pentenyl, hexenyl and the like.

Preferable examples of "aryl" include phenyl, tolyl, xylyl, cumenyl, mesityl, naphthyl and the like.

Preferable examples of the protective group for "protected hydroxy" and "protected amino" include 1-(loweralkylthio)(lower)alkyl such as lower alkylthiomethyl (e.g., methylthiomethyl, ethylthiomethyl, propylthiomethyl, isopropylthiomethyl, butylthiomethyl, isobutylthiomethyl, hexylthiomethyl and the like), with more preference given to C₁ - C₄ alkylthiomethyl and most preference given to methylthiomethyl;

tri-substituted silyl such as tri(lower)alkylsilyl (e.g., trimethylsilyl, triethylsilyl, tributylsilyl, tert-butyl dimethylsilyl, tri-tert-butylsilyl and the like), and lower alkyldiarylsilyl (e.g., methyldiphenylsilyl, ethyldiphenylsilyl, propyldiphenylsilyl, tert-butyldiphenylsilyl and the like, with more preference given to tri(C₁ - C₄)alkylsilyl and C₁ - C₄ alkyldiphenylsilyl, and most preference given to tert-butyl-dimethylsilyl, tert-butyldiphenylsilyl;

acyl such as fatty acyl derived from carboxylic acid, sulfonic acid and carbamic acid, fatty acyl substituted by aromatic acyl and aromatic, and the like.

The fatty acyl is exemplified by lower alkanoyl optionally having 1 or more suitable substituent(s) (e.g., carboxy) such as formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, carboxyacetyl, carboxypropionyl, carboxybutyryl, carboxyhexanoyl and the like ;

cyclo(lower)alkyloxy(lower)alkanoyl optionally having 1 or more suitable substituent(s) (e.g., lower alkyl) such as cyclopropyloxyacetyl, cyclobutyloxypropionyl, cycloheptyloxybutyryl, mentyloxyacetyl, mentyloxypropionyl, mentyloxybutyryl, mentyloxypentanoyl, mentyloxyhexanoyl and the like, camphorsulfonyl ;

lower alkylcarbamoyl having one or more suitable substituent(s) such as carboxy or protected carboxy and the like, such as carboxy(lower)alkylcarbamoyl (e.g., carboxymethylcarbamoyl, carboxyethylcarbamoyl, carboxypropylcarbamoyl, carboxybutylcarbamoyl, carboxypentylcarbamoyl, carboxyhexylcarbamoyl) and

tri(lower)alkylsilyl(lower)alkyloxycarbonyl(lower)alkylcarbamoyl (e.g.,
 trimethylsilylmethoxycarbonylethylcarbamoyl,
 trimethylsilylethoxycarbonylpropylcarbamoyl,
 triethylsilylethoxycarbonylpropylcarbamoyl, tert-butyl
 5 dimethylsilylethoxycarbonylpropylcarbamoyl,
 trimethylsilylpropoxycarbonylbutylcarbamoyl).

Aromatic acyl is exemplified by aroyl optionally having suitable
 substituent(s) (e.g., nitro), such as benzoyl, toluoyl, xyloyl, naphthoyl, nitrobenzoyl,
 dinitrobenzoyl, nitronaphthoyl and the like ; and
 10 arenesulfonyl optionally having one or more suitable substituent(s) (e.g., halogen),
 such as benzenesulfonyl, toluenesulfonyl, xylenesulfonyl, naphthalenesulfonyl,
 fluorobenzenesulfonyl, chlorobenzenesulfonyl, bromobenzenesulfonyl,
 iodobenzenesulfonyl and the like.

The aliphatic acyl substituted by aromatic group may be, for example,
 15 ar(lower)alkanoyl optionally having one or more suitable substituent(s) (e.g., lower
 alkyloxy or trihalo(lower)alkyl and the like), wherein specific examples are
 phenylacetyl, phenylpropionyl, phenylbutyryl, 2-trifluoromethyl-2-methoxy-2-
 phenylacetyl, 2-ethyl-2-trifluoromethyl-2-phenylacetyl, 2-trifluoromethyl-2-
 propoxy-2-phenylacetyl and the like.

20 Of the above-mentioned acyl, more preferable acyl includes C₁ - C₄ alkanoyl
 optionally having carboxy, cyclo(C₅ - C₆)alkyloxy(C₁ - C₄)alkanoyl having two (C₁ -
 C₄)alkyl in the cycloalkyl moiety, camphorsulfonyl, carboxy (C₁ -
 C₄)alkylcarbamoyl, tri(C₁ - C₄)alkylsilyl(C₁ - C₄)alkyloxycarbonyl(C₁ -
 C₄)alkylcarbamoyl, benzoyl optionally having 1 or 2 nitro groups, and
 25 benzenesulfonyl having halogen, phenyl(C₁ - C₄)alkanoyl having C₁ - C₄ alkyloxy
 and trihalo(C₁ - C₄)alkyl. Of these, most preferred are acetyl, carboxypropionyl,
 mentyloxyacetyl, camphorsulfonyl, benzoyl, nitrobenzoyl, dinitrobenzoyl,
 iodobenzenesulfonyl, 2-trifluoromethyl-2-methoxy-2-phenylacetyl and the like.

Preferable examples of the "heterocyclic group consisting of saturated or
 30 unsaturated 5 or 6-membered ring having nitrogen atom, sulfur atom and/or
 oxygen atom" are pyrrolyl, tetrahydrofuryl and the like.

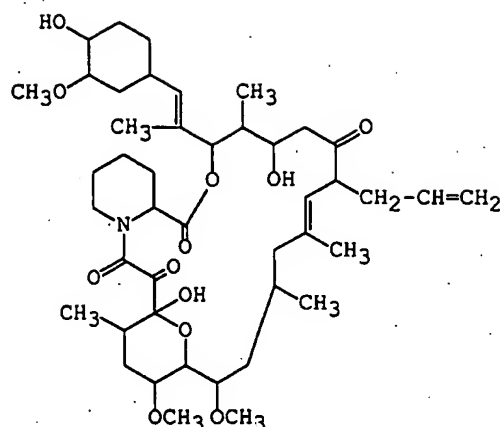
The "heteroaryl optionally having a suitable substituent moiety" of the
 "heteroaryloxy optionally having a suitable substituent" is that exemplified for R¹ of

the compound of the formula I of EP-A-532,088, with preference given to 1-hydroxyethylindol-5-yl. The disclosure is incorporated hereinto by reference.

The tricyclo compound (I) and a pharmaceutically acceptable salt thereof to be used in the present invention have superior IL-2 inhibitory action and immunosuppressive action, antibacterial action and other pharmacological activity, so that they are useful for the prophylaxis and treatment of rejection in organ or tissue transplantation, graft versus host reaction, autoimmune diseases, infectious diseases and the like, as noted, together with the production method thereof, in, for example, EP-A-184162, EP-A-323042, EP-A-423714, EP-A-427680, EP-A-465426, EP-A-480623, EP-A-532088, EP-A-532089, EP-A-569337, EP-A-626385, WO89/05303, WO93/05058, WO96/31514, WO91/13889, WO91/19495, WO93/5059 and the like, all of these publications are hereby incorporated by reference.

In particular, the compounds called FR900506 (=FK506), FR900520 (Ascomycin), FR900523 and FR900525 are produced by the genus *Streptomyces*, such as *Streptomyces tsukubaensis*, No. 9993 (depository : National Institute of Bioscience and Human-Technology Agency of Industrial Science and Technology, the Ministry of International Trade and Industry, 1-3, Higashi 1-chome, Tsukuba-shi, Ibaraki-ken, Japan (formerly : Fermentation Research Institute, Agency of Industrial Science and Technology, the Ministry of International Trade and Industry), date of deposit : October 5, 1984, deposit number : FERM BP-927 or *Streptomyces hygroscopicus subsp. Yakushimaensis*, No. 7238 (depository : National Institute of Bioscience and Human-Technology Agency of Industrial Science and Technology, 1-3, Higashi 1-chome, Tsukuba-shi, Ibaraki-ken, Japan (formerly : Fermentation Research Institute, Agency of Industrial Science and Technology, the Ministry of International Trade and Industry), date of deposit : January 12, 1985, deposit number : FERM BP-928 (EP-A-0184162), and the compound of the following formula, FK506 (general name : Tacrolimus) is a representative compound.

30



Chemical name : 17-allyl-1,14-dihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.0^{4,9}]octacos-18-ene-2,3,10,16-tetraone

Of the tricyclo compounds (I), more preferred is a compound wherein adjacent pairs of R³ and R⁴, and R⁵ and R⁶ each independently form another bond optionally between carbon atoms binding with the members of said pairs ;

10 R⁸ and R²³ each independently show hydrogen atom ;

R⁹ is hydroxy ;

R¹⁰ is methyl, ethyl, propyl or allyl ;

X is (hydrogen atom, hydrogen atom) or oxo ;

Y is oxo ;

15 R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹ and R²² each independently show methyl ;

R²⁴ is 3-R²⁰-4-R²¹-cyclohexyl,

wherein R²⁰ is hydroxy, alkyloxy or -OCH₂OCH₂CH₂OCH₃, and

R²¹ is hydroxy, -OCN, alkyloxy, heteroaryloxy having suitable substituent,

-OCH₂OCH₂CH₂OCH₃, protected hydroxy, chloro, bromo, iodo,

20 aminooxalyloxy, azide, p-tolyloxythiocarbonyloxy

or R²⁵R²⁶CHCOO- wherein R²⁵ is optionally protected hydroxy as desired,

or protected amino, and R²⁶ is hydrogen atom or methyl), or R²⁰ and R²¹ in

combination form an oxygen atom of epoxide ring; and

n is 1 or 2.

Particularly preferable tricyclo compound (I) include, besides FK506, Ascomycin derivatives such as halogenated derivative of 33-epi-chloro-33-desoxy Ascomycin described in Example 66a of EP-A-427,680 and the like.

Other preferable IL-2 inhibitors (macrolide compounds) include

- 5 Rapamycin described in MERCK INDEX, 12 edition, No. 8288 and derivatives thereof. Preferable examples thereof include O-substituted derivative described at page 1 of WO95/16691, formula A, wherein the 40th hydroxy is -OR₁ (wherein R₁ is hydroxyalkyl, hydroalkyloxyalkyl, acylaminoalkyl and aminoalkyl), such as 40-O-(2-hydroxy)ethyl Rapamycin, 40-O-(3-hydroxy)propyl Rapamycin, 40-O-[2-
10 (2-hydroxy)ethoxy]ethyl Rapamycin and 40-O-(2-acetaminoethyl)-Rapamycin. These O-substituted derivatives can be produced by reacting, under appropriate conditions, Rapamycin (or dihydro or deoxo Rapamycin) and an organic radical bound with leaving group (e.g., RX wherein R is an organic radical desirable as O-substituent, such as alkyl, allyl and benzyl moiety, and X is a leaving group such
15 as CCl₃C(NH)O and CF₃SO₃). The conditions are: when X is CCl₃C(NH)O, acidic or neutral conditions, such as in the presence of trifluoromethanesulfonic acid, camphorsulfonic acid, p-toluenesulfonic acid or their corresponding pyridinium or substituted pyridinium salt, and when X is CF₃SO₃, in the presence of a base such
20 as pyridine, substituted pyridine, diisopropylethylamine and pentamethylpiperidine. The most preferable Rapamycin derivative is 40-O-(2-hydroxy)ethyl Rapamycin as disclosed in WO94/09010, which is hereby incorporated into the specification by reference.

- The pharmaceutically acceptable salt of tricyclo compound (I), Rapamycin and derivatives thereof are nontoxic and pharmaceutically acceptable
25 conventional salts, which are exemplified by salts with inorganic or organic base such as alkali metal salt (e.g., sodium salt, potassium salt and the like), alkaline earth metal salt (e.g., calcium salt, magnesium salt and the like), ammonium salt, and amine salt (e.g., triethylamine salt, N-benzyl-N-methylamine salt and the like).

- In the IL-2 inhibitor of the present invention, particularly macrolide
30 compound, one or more pairs of stereoisomers, such as optical isomers and geometric isomers, may be included due to conformer or asymmetric carbon atom and double bond. Such conformers and isomers are also encompassed in the present invention. In addition, macrolide compounds can form solvates, which

case is also encompassed in the present invention. Preferable solvate is exemplified by hydrates and ethanolates.

Other IL-2 inhibitors are known from MERCK INDEX, 12th ed., No. 2821, US Patent Nos. 4,117,118, 4,215,199, 4,288,431, 4,388,307, *Helv. Chim. Acta*, 60, 1568 (1977) and 65,1655 (1982) and *Transplant. Proc.* 17, 1362 (1985) and the like. Specifically, they are cyclosporins such as cyclosporin A, B, C, D, E, F and G and derivatives thereof. Particularly preferred is cyclosporin A. These are hereby incorporated into the specification by reference.

The tricyclo compound (I), pharmaceutically acceptable salt thereof, cyclosporins and derivatives thereof can be classified as "IL-2 production inhibitor" that inhibit production of IL-2. Rapamycin and derivative thereof can be classified as "IL-2 signal transduction inhibitor" that inhibit transmission of IL-2 signal.

In the present invention, visual cell function disorder means the state where visual cell of retina is suffering from disorder in the function for a certain reason, which can be specifically confirmed by the variation of peak latency or amplitude of a-wave in ERG as compared to those in the normal state. Inasmuch as the visual cell function disorder is caused by various retinal disorders such as degenerative retinopathy, retinochoroidal disorders and the like, the agent of the present invention for the treatment of visual cell function disorder can be used for treating retinopathy. In particular, the agent for treating visual cell function disorder of the present invention has superior action of improving visual cell function disorder, as is evident from the experimental example to be mentioned later, in ischemic retinopathy models, and can be used for the treatment of ischemic retinopathy. The ischemic retinopathy is caused by various reasons. For example, retinovascular diseases are caused by systemic disease, such as diabetes, hypertension and arteriosclerosis, and are exemplified by diabetic retinopathy, fundus hypertonicus, as well as local vascular disorders in retina, such as central retinal artery occlusion, central retinal vein thrombosis, retinal peripheral vascular occlusion, retinopathy of prematurity and the like.

The treatment in the context of the present invention includes any management such as prevention, treatment, alleviation of symptom, reduction of symptoms, prevention of progression and the like.

The interleukin 2 inhibitor to be used in the present invention can be used as a pharmaceutical agent for human and animals, and can be administered systemically or locally by oral administration, intravenous administration (inclusive of transfusion), subcutaneous administration, rectal or vaginal administration, administration to local site of the eye (inclusive of eye ointment). In consideration of systemic influence, significant expression of the effect and the like, it is particularly preferably used in the form for local administration to the eye.

The dose of the interleukin 2 inhibitor varies depending on the kind, age, body weight of the administration object such as human and animal, condition to be treated, desired therapeutic effect, administration route, treatment method, treatment period and the like. Generally, when it is administered systemically, the dose is about 0.0001 – 1000 mg, preferably 0.001 – 500 mg, which is given in a single dose or 2 to 4 doses a day or in a sustained manner. When it is administered locally to the eye, a preparation containing the active ingredient in a proportion of 0.001 – 10.0 w/v%, preferably 0.005 – 5.0 w/v%, is applied several times a day per eye, preferably instilled or applied 1 to 6 times a day.

According to the present invention, an interleukin 2 inhibitor, which is an active ingredient, can be administered alone or in combination with other pharmacologically active components. When administered after formulating a preparation, it can be administered as a preparation produced by a conventional method. The dosage form may be, for example, eye drop, eye ointment, powder, granule, tablet, capsule, injection, ointment and the like, with particular preference given to eye drop and eye ointment. Such preparation can be produced according to a conventional method. Of such preparations, an oral preparation is preferably a solid solution preparation produced in the same manner as in the preparation of EP-A-0240773. When an eye drop is desired, an eye drop as described in EP-A-0406791 is preferable. When desired, additives generally used for eye drop such as isotonicizing agent (e.g., sodium chloride), buffer (e.g., boric acid, phosphoric acid-sodium hydrogen, sodium dihydrogenphosphate and the like), preservative (e.g., benzalkonium chloride, benzetonium chloride, chlorobutanol and the like), tackifier [e.g., sugar (lactose, mannitol, maltose sugar and the like), hyaluronic acid (sodium hyaluronate, potassium hyaluronate and the like), a salt thereof, mucopolysaccharide (chondroitin sulfate and the like),

sodium polyacrylate, vinyl carboxy polymer, crosslinked polyacrylate, and the like] may be added. These are hereby incorporated into the specification by reference.

The present invention is explained in more detail in the following by way of Examples, to which the present invention is not limited.

5 • Examples

Experimental Example 1 Effect on changes in ERG of rats with retinal ischemia

An ischemic state was induced by ligating the retinal blood vessel of rat and reperfusion to make ischemic retinopathy model in rat, with which the effect on changes in retinal potential was tested.

10 (1) Test animal

Long Evans colored rats (male, 7- or 8-week-old when received : body weight 200 - 250 g) were prebred for 8 days and the animals free of abnormality in general conditions, such as body weight, were used for the test.

(2) Test substance and administration method

15 As the active ingredient in the present invention, FK506 was used and the following 0.1% eye drop (suspension) was used as a test drug.

Test drug

Suspension having the following composition which was prepared in the same manner as in EP-A-0406791 (Example 6)

20	FK506	1.0 mg
	polyvinyl alcohol	7.0 mg
	disodium hydrogenphosphate 12 hydrate	0.05 mg
	sodium dihydrogenphosphate 2 hydrate	0.76 mg
	phosphoric acid	appropriate amount
25	sodium hydroxide	appropriate amount
	sodium chloride	8.56 mg
	benzalkonium chloride	0.1 mg
	injectable water	appropriate amount

30	Total amount	1 ml
----	--------------	------

As the control, the base agent of an eye drop without the active ingredient was used. The test drug was instilled to the eye by 10 μ l/eye using a micropipette

3 times a day (8 : 00, 13 : 00, 18 : 00) from day 1 to day 7 of the test. The control agent was also administered by instillation in the same manner.

(1) preparation of ischemic retinopathy model

At day 8 of the test, the rats were anesthetized by intraperitoneal administration of diazepam (0.625 mg/kg), and pentobarbital (20 mg/kg) and a part of periorbita was removed from the side. A pedicle consisting of optic nerve, ophthalmic artery and ophthalmic vein was removed and the whole pedicle was ligated to cause ischemia. The ischemia was continued for 45 minutes and reperused by releasing the ligation.

10 (2) ERG determination

The apparatus and parameter were standardized by the following.
"Standard for Clinical Electroretinography" (International Standardization Committee)

Apparatus :

15 The Electrophysiologic Personal Interfaced Computer-2000 (LKC Technologies Incorporated)

ERG determination parameter :

amplifier

high pass filter : 500 Hz

20 low pass filter : 0.3 Hz

notch filter : off

amplitude : 50 μ V/division (maximum 1500 μ V)

time : 20 ms/division (maximum 2500 ms)

cornea electrode

25 impedance : 10 to 20 K Ω

optical stimulation

single flash : 15 ms

intensity : 2.289 cd. s.m⁻²

ganzfeld

30 filter : none

ERG was determined with the lapse of time before and after ischemia under the above-mentioned conditions.

(3) results

Taking the ERG before ischemia as 100%, the ratio thereto of the peak latency of the a-wave after reperfusion was determined. It disappeared immediately after reperfusion. The results are shown in Table 1.

Table 1

Administration group	(n)	a-wave peak latency (% average \pm SD)		
		60 min after reperfusion	90 min after reperfusion	120 min after reperfusion
Control drug	(8)	195.6 \pm 53.5	190.8 \pm 55.3	191.9 \pm 60.4
Test drug	(8)	137.1 \pm 47.1*	141.6 \pm 44.8*	134.4 \pm 31.6*

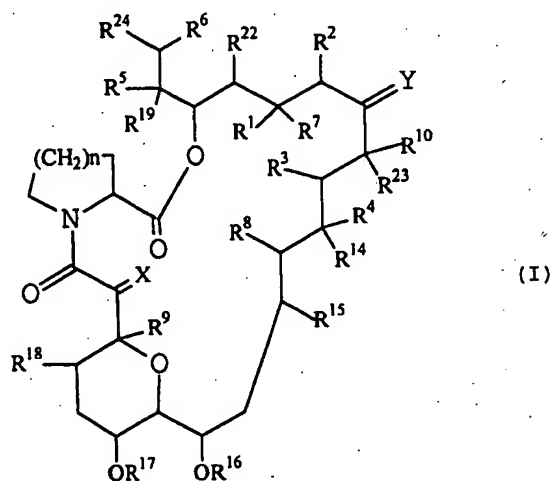
* P<0.05 (comparison to control drug by ANOVA detection)

5 The a-wave peak latency disappeared immediately after reperfusion, but peak latency was prolonged with the lapse of time thereafter. As is evident from Table 1, the test drug administration group significantly suppressed the prolongation of the a-wave peak latency as compared to the control drug group.

10 This application is based on application No. 60/113,939 filed in United States of America, the content of which is incorporated hereinto by reference.

CLAIMES

1. An agent for treating visual cell function disorder comprising an interleukin 2 inhibitor as an active ingredient.
2. The agent of claim 1, wherein the interleukin 2 inhibitor is a macrolide compound or a cyclosporin.
3. The agent of claim 2, wherein the macrolide compound is a tricyclo compound (I) of the following formula



10

wherein adjacent pairs of R^1 and R^2 , R^3 and R^4 , and R^5 and R^6 each independently

- a) consist of two adjacent hydrogen atoms, wherein R^2 is optionally alkyl, or
- b) form another bond optionally between carbon atoms binding with the members of said pairs ;

- 15 R^7 is hydrogen atom, hydroxy, protected hydroxy, or alkyloxy, or optionally form oxo with R^1 ;

R^8 and R^9 each independently show hydrogen atom or hydroxy ;

R^{10} is hydrogen atom, alkyl, alkyl substituted by one or more hydroxy, alkenyl, alkenyl substituted by one or more hydroxy or alkyl substituted by oxo ;

- 20 X is oxo, (hydrogen atom, hydroxy), (hydrogen atom, hydrogen atom), or a group of the formula $-CH_2O-$;

Y is oxo, (hydrogen atom, hydroxy), (hydrogen atom, hydrogen atom), or a group of the formula $N-NR^{11}R^{12}$ or $N-OR^{13}$;

R¹¹ and R¹² each independently show hydrogen atom, alkyl, aryl or tosyl ;
R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²² and R²³ each independently show hydrogen atom or alkyl ;

R²⁴ is a ring that is optionally substituted and optionally contain one or more
5 hetero atom(s) ; and

n is 1 or 2,

wherein Y, R¹⁰ and R²³ optionally show, together with the carbon atom they bind with, a saturated or unsaturated 5 or 6-membered heterocyclic group containing nitrogen atom, sulfur atom and/or oxygen atom, the
10 heterocyclic group being optionally substituted by one or more group(s) selected from the group consisting of alkyl, hydroxy, alkyloxy, benzyl, a group of the formula -CH₂Se(C₆H₅), and alkyl substituted by one or more hydroxy,

or a pharmaceutically acceptable salt thereof.

15

4. The agent of claim 2 or claim 3, wherein the macrolide compound is FK506.

5. The agent of any of claim 1 to claim 4, which is used for the treatment of retinopathy.

20

6. The agent of claim 5, wherein the retinopathy is ischemic retinopathy.

7. The agent of claim 6, wherein the ischemic retinopathy is diabetic retinopathy.

25 8. The agent of any of claim 1 to claim 7, which is in the form of a preparation for local administration to the eye.

9. A method for treating visual cell function disorder, comprising administering an effective amount of interleukin 2 inhibitor to a subject in need of the treatment
30 of visual cell function disorder.

10. Use of interleukin 2 inhibitor for the production of a pharmaceutical composition for the treatment of visual cell function disorder.

INTERNATIONAL SEARCH REPORT

Inten. natl Application No

PCT/JP 99/07161

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K38/13 A61K31/436 A61P27/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 99 00129 A (DREYER EVAN B) 7 January 1999 (1999-01-07) * See Table 1, (page 2) FK-506 * page 8; claims	1-10
X	WO 94 13275 A (MASSACHUSETTS EYE AND EAR INFI ;CHILDRENS MEDICAL CENTER (US)) 23 June 1994 (1994-06-23) * See table 2, second page, FK-506 * page 5, line 30-33	1-10
X	WO 96 00073 A (MASSACHUSETTS EYE AND EAR INFI ;DREYER EVAN B (US)) 4 January 1996 (1996-01-04) * See page 36, table 5 * claims	1-10
	-/-	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

31 May 2000

Date of mailing of the international search report

14/06/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 851 epo nl,
Fax: (+31-70) 340-3018

Authorized officer

Veronese, A

INTERNATIONAL SEARCH REPORT

Inter. Appl. Application No

PCT/JP 99/07161

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 92 03049 A (UNIV NEW YORK) 5 March 1992 (1992-03-05) claim 4 page 8, line 6 claims 4,11,12	1-5,8-10
E	WO 00 09109 A (GUILFORD PHARM INC) 24 February 2000 (2000-02-24) claims 1,4,5,7,17	1,2,5-10
X	EP 0 532 862 A (UNIV LOUISVILLE RES FOUND) 24 March 1993 (1993-03-24)	1,2,5-10
Y	column 1, line 32-44; claims 1-10; examples	6-8
P,X	WO 99 34830 A (MA & TCARON ;GALENA A S (CZ); STUCHLIK JOSEF (CZ); STUCHLIK MILAN) 15 July 1999 (1999-07-15) page 2, paragraphs 1-4; claims page 1, paragraphs 2,3	1-4,8-10
X	KIRYU, J. (1) ET AL: "In vivo evaluation of the inhibitory effects of tacrolimus (FK506) on leukocyte accumulation during retinal ischemia reperfusion injury." IOVS, (MARCH 15, 1998) VOL. 39, NO. 4, PP. S273. MEETING INFO.: ANNUAL MEETING OF THE ASSOCIATION FOR RESEARCH IN VISION AND OPHTHALMOLOGY FORT LAUDERDALE, FLORIDA, USA MAY 10-15, 1998 ASSOCIATION FOR RESEARCH IN VISION AND OPHTHALMOLOGY., XP000913707	1-5,9,10
Y	abstract	6-8
X	KIKUCHI M ET AL: "Protective effects of FK506 against glutamate-induced neurotoxicity in retinal cell culture." INVESTIGATIVE OPHTHALMOLOGY AND VISUAL SCIENCE, (1998 JUN) 39 (7) 1227-32., XP000913706	1-5,9,10
Y	the whole document	6-8
X	TSUJIKAWA, AKITAKA ET AL: "Tacrolimus (FK506) attenuates leukocyte accumulation after transient retinal ischemia" STROKE (1998), 29(7), 1431-1438 , XP000913599	1-5,9,10
Y	the whole document	6-8
	-/-	

INTERNATIONAL SEARCH REPORT

Intern. Appl. No.

PCT/JP 99/07161

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MARTIN, DANIEL F. ET AL: "Synergistic effect of rapamycin and cyclosporin A in the treatment of experimental autoimmune uveoretinitis" J. IMMUNOL. (1995), 154(2), 922-7 , XP000907419 the whole document	1,2,5-10
X	PEARSON, P. A. (1) ET AL: "Sustained delivery of cyclosporine (CsA) and dexamethasone (DEX) in the treatment of experimental proliferative vitreoretinopathy." INVESTIGATIVE OPHTHALMOLOGY & VISUAL SCIENCE, (1994) VOL. 35, NO. 4, PP. 1923. MEETING INFO.: ANNUAL MEETING OF THE ASSOCIATION FOR RESEARCH IN VISION AND OPHTHALMOLOGY SARASOTA, FLORIDA, USA MAY 1-6, 1994 , XP000913593	1,2,5-10
Y	abstract	6-8
X	STRIPH, GERALD ET AL: "Retina S antigen-induced uveitis. The efficacy of cyclosporine and corticosteroids in treatment" ARCH. OPHTHALMOL. (CHICAGO) (1986), 104(1), 114-17 , XP000913594 the whole document	1,2,5-10

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP 99/07161

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

The wording "an agent for treating visual cell function disorder comprising an interleukin 2 inhibitor" and the generic term "macrolide compound" relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Moreover, present claim 1 relates to compounds defined by reference to a pharmacological mechanism of action "compound which inhibits interleukin 2". The definition of compounds by reference to a pharmacological mechanism in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is impossible to fully compare the parameters the applicant has chosen to employ with what is set out in the prior art.

Also the definition "visual cell function disorder" is considered obscure, not defining a specific disease recognized in the art to which the invention belongs.

Therefore, present claim 1 and 2 and the corresponding dependent claims, relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, concise, supported and disclosed, namely for the compounds defined by Markush formula (I) in claim 3 and the compounds explicitly mentioned in the description at pages 8-11 and in claim 4, in respect to the diseases explicitly mentioned in claims 5-7 and in the description at pages 11, with due regard to the general idea underlying the application.

All claims 1 to 10 have been searched incompletely.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. Patent Application No

PCT/JP 99/07161

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9900129 A	07-01-1999	AU 7967298 A EP 0994709 A	19-01-1999 26-04-2000
WO 9413275 A	23-06-1994	US 5922773 A AU 683634 B AU 5741494 A CA 2150933 A EP 0671910 A JP 8506807 T	13-07-1999 20-11-1997 04-07-1994 23-06-1994 20-09-1995 23-07-1996
WO 9600073 A	04-01-1996	US 5597809 A AU 711652 B AU 2819695 A CA 2192209 A EP 0797442 A JP 10502340 T	28-01-1997 21-10-1999 19-01-1996 04-01-1996 01-10-1997 03-03-1998
WO 9203049 A	05-03-1992	AT 147936 T DE 69124380 D DE 69124380 T EP 0544802 A US 5514714 A	15-02-1997 06-03-1997 14-08-1997 09-06-1993 07-05-1996
WO 0009109 A	24-02-2000	NONE	
EP 0532862 A	24-03-1993	AT 133336 T AU 653415 B AU 2035092 A CA 2074641 A CZ 285660 B DE 69207847 D DE 69207847 T DK 532862 T ES 2083030 T HK 1005705 A HU 211218 B IL 102414 A JP 2568962 B JP 5194212 A MX 9204381 A NZ 243679 A SK 230792 A RU 2048812 C US 5387589 A ZA 9204953 A	15-02-1996 29-09-1994 28-01-1993 26-01-1993 13-10-1999 07-03-1996 30-05-1996 19-02-1996 01-04-1996 22-01-1999 28-11-1995 04-08-1996 08-01-1997 03-08-1993 01-02-1993 24-06-1997 08-05-1996 27-11-1995 07-02-1995 28-04-1993
WO 9934830 A	15-07-1999	CZ 9704237 A AU 1481399 A	14-07-1999 26-07-1999